to support consistent reporting of dose-volume data and NTCP-models. However, further improvement of delineation quality can be achieved by training and education, and a more consistent use of these guidelines. References: 1. Brouwer et al., Radiother Oncol 2015 aug 13 (ahead of print). 2. Steenbakkers et al., Int J Radiat Oncol Biol Phys. 2006;64:435-48. 3. Hanna GG et al., Clin Oncol. 2010;22:515–525.

Symposium: DNA repair inhibition and radiotherapy: moving towards clinic

SP-0296
Challenges in combining radiation and chemo-radiation with PARP inhibitors

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Locally advanced NSCLC is a heterogeneous disease both with regard of the staging and the tumor behavior. In order to improve outcome, combinations of radiation (RT) with cytotoxic drugs to modulate RT-induced cytotoxicity were introduced and are now standard of care. Also in many other malignancies combined modality has shown to improve outcome and has become standard of care. These treatment options are in particular of benefit in patients that can tolerate such treatment regimens. Improvements have been made both in chemotherapy and the radiotherapy. However, co-morbidities and the observed increased normal tissue toxicity limit the use of potent chemoradiotherapy approaches. In order to enhance the therapeutic window, tumor targeted strategies are needed to allow tumor radiosensitization while not affecting normal tissue. This warrants the evaluation of the potential of novel targeted radiosensitizers with tumor targeted properties. The main mechanism by which both radiation and cisplatin kill tumor cells is by an accumulation of un- or misrepaired DNA damage. PARP inhibitors increase radiation and chemotherapy (cisplatin) response in preclinical studies including lung cancer models. PARP inhibitors have been shown to specifically kill homologous recombination deficient tumor cells as single agent. ATM mutations are expected to affect DSB repair and homologous recombination status therefore amplifying damage induced by the combined PARP inhibitor radiation treatment. Thus tumor targeted treatment and radio-chemosensitization in lung cancer could be achieved in the presence of frequently observed ATM gene mutations in lung cancer. Olaparib exhibits low systemic toxicity profiles when given as monotherapy. When combined with cisplatin and RT enhanced toxicity is anticipated, necessitating careful dose- and schedule-finding and development and validation of supporting pharmacodynamic markers. Such approach could also serve as a template for other promising radiosensitizers, for example DNA-PK, ATM and ATR inhibitors of kinases that are key mediators of the so-called DNA damage response (DDR).

SP-0297
Results of phase I trials combining PARP inhibition and radiotherapy in multiple sites

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Increased understanding of the molecular mechanisms underlying tumour and normal cell radiosensitivity has led to the identification of a variety of potential targets for rational intervention. These are based on the “hallmarks of cancer”, eight biological capabilities acquired during the multistep development of human tumours. Among these, targeting the DNA damage response represents an attractive strategy, especially in tumours that contain mutations in specific components of the DNA repair pathway, such as BRCA1 and BRCA2. In addition to their use as single agents, inhibitors of the DNA damage response, when combined with radiation could increase tumour response while sparing the normal tissue.

Poly(ADP-ribose) polymerase (PARP) inhibitors affect DNA repair and thus are good candidates for combined use with DNA damaging agents. Indeed, PARP inhibitors increase radiation and chemotherapy responses in preclinical studies. As a single agent they have been shown to specifically kill homologous recombination (HR) deficient tumour cells. A large variety of tumour-specific mutations, such as in BRCA or ATM, affect double strand break repair and HR status and therefore amplify the damage induced by the combined PARP inhibitor radiation treatment. We found that the PARP inhibitor olaparib induced radiosensitisation in mouse breast cancer cells and in a panel of human head and neck cancer cell lines at much lower doses than those required for its single agent activity. Importantly, at these low doses olaparib prevented PAR induction by radiation. Also, the extent of radiosensitisation by olaparib depended on the integrity of the HR pathway, as witnessed by the difference in olaparib dose required to induce radiosensitisation in BRCA2-deficient versus BRCA2-complemented cells.

We have designed 3 phase I-II studies evaluating the safety and tolerability of olaparib, in combination with radiotherapy in locally advanced breast cancer, non-small cell lung cancer and head and neck cancer. Dose-escalation according to the TITE-CRM design allows the evaluation of late toxicity and ensures continuous patient accrual. In support of these trials, biomarkers for the radiosensitisation efficacy of PARP inhibitors have been developed and are evaluated. Tumour and normal tissue samples are collected from all patients to measure PARP inhibition and γH2AX foci formation. These measurements will help to guide the dose-escalation strategy used in these trials.

SP-0298
Phase I Results of PARPi (Olaparib) + RT + Cetuximab in LAHNSCC

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DNA repair within cancers contributes to radioresistance and is a concept across all histology’s. Cancer cells employ rapid and efficient methods for repairing damaged single and double strand DNA breaks from radiation and chemotherapy. Can we take advantage of this survival mechanism? One strategy incorporates the use of poly(ADP-ribose) polymerase (PARP) inhibitors. What do we know about PARP? PARP inhibition sparked interest in oncology based in part on the concept of “synthetic lethality” in which cancer cells with pre-existing deficiencies in homologous-recombination pathways (e.g. BRCA mutations) exhibit highly selective cytotoxicity to single agent PARP inhibitors in contrast to normal cells – a differentiation that radiation oncologists find attractive and might provide an opportunity with radiation based studies for locally advanced cancers. Building upon the synthetic lethality story, PARP inhibitors show promise as radiosensitizers by directly preventing cancer cells from repairing stress induced DNA damage. In the preclinical setting, our data suggested enhanced sensitivity to PARP(I) monotherapy as well as when combined with radiation across a variety of HNSCC lines known to be HPV negative many groups have shown the ability of PARP inhibitors to sensitize a variety of histology’s, both p53 wild type and null, to radiation in both in vitro and in vivo settings. The data seems to suggest that the levels of PARP inhibition required to enhance radiation may be significantly lower than when used